Familial risk estimation in systemic sclerosis

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Abstract

Background: Familial systemic sclerosis has been rarely reported. Assumptions have therefore been made implying no familial disease aggregation. This study critically challenges the assumption using a methodical population-based epidemiological approach to quantify the prevalence and characteristics of familial systemic sclerosis.

Methods: In this retrospective cohort study the systemic sclerosis prevalence in first degree family members was compared between 715 systemic sclerosis patients (710 families) and 371 randomly ascertained age and gender group-matched general practice controls (371 families). These data, obtained by telephone questionnaire (living patients) or medical records review (deceased patients and untraceable patients of unknown living status), were validated, where necessary, and expressed in terms of relative risk, absolute risk and population point prevalence.

Results: Systemic sclerosis affecting first degree members was validated in ten of 710 families. Reporting of systemic disease in another four more distant family members, and the co-occurrence of systemic and localised disease in three families was also documented.

Observed and expected disease subtype concordance was 80% (44-97%) and 68% respectively and the female predominance among familial cases was similar to that for non-familial disease. The risk of disease in a subsequent first degree relative was compared to the risk in an initial first degree family member. Its estimated magnitude was wide (11-158). However, use of population prevalence data to determine the expected number of systemic sclerosis patients in the negative cohorts' families suggests

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the higher estimate is more realistic. Despite the high magnitude, the absolute disease risk in first degree family members remained low – approximating 1%. The population prevalence of familial systemic sclerosis approximated 1.4/million.

Conclusions: This study substantially increases the otherwise small list of documented instances of familial systemic sclerosis. More importantly, it quantifies the risk for the first time, ranking it as the disease's most powerful determinant identified to date. (Aust NZ J Med 1999; 29: 36-41.)

Key words: Systemic sclerosis, familial risk.

INTRODUCTION

'There is no evidence in the literature to suggest an inordinate degree of familial aggregation of (systemic sclerosis).'[1]

'. . . the number of (systemic sclerosis) probands with an affected relative is extremely small . . .'[2]

Although reports of familial systemic sclerosis occur sporadically throughout the medical literature[3-18] they are remarkable for their rarity. Together with findings of disease discordance in monozygotic twins, with one or possibly two exceptions,[19,20] these have been interpreted to imply a very low genetic contribution to systemic sclerosis aetiology. However, it is unclear whether this lack of reporting[1] reflects truly low familial rates in a disease of low prevalence or whether the lack of reporting reflects underascertainment of familial cases.

Aims

As part of a population-based epidemiological study of systemic sclerosis a systematic approach was made to quantify the prevalence and characteristics of familial disease. Also, given one affected family member, the study also estimated both the relative and absolute risk of systemic sclerosis in subsequent first degree family members. Although preliminary results from this study have been reported,[25,26] the definitive results form the basis of this paper.

METHODS

The patients were part of a population-based study investigating the distribution and determinants of systemic sclerosis within Sydney between 1974 and 1988.[27] One study component comprised quantitation of familial disease.

Study Design

It employed a retrospective cohort study design in which the outcome, systemic sclerosis in another family member, was compared between two cohorts, systemic sclerosis patients and patients from general medical practices within Sydney.

Positive Cohort

The positive cohort comprised 715 patients representing 710 families. Of these, 340 patients (from 338 families) were interviewed while the remainder, with few exceptions, were either deceased, untraceable or of unknown living status. Systemic sclerosis patients were eligible for the study if they had a premortem clinical diagnosis of systemic sclerosis or CREST syndrome and their disease characteristics satisfied either the American Rheumatism Association Preliminary Classification Criteria[28] or criteria designed specifically for this study. The latter were devised in order to include a subset of CREST patients with skin involvement confined to the digits. These criteria were sclerodactyly and at least two of: Raynaud's, oesophageal dysmotility, calcinosis, telangiectasia, or an elevated antinuclear antibody.

Negative Cohort

The general practice cohort, age- and gender group-matched to the cases, were otherwise randomly selected from each of 28 Sydney general medical practices, the practices themselves having been randomly selected from the Royal Australian College of General Practitioners' medical practitioner database. The controls comprised 371 patients from 371 families. All 371 were interviewed.

The mode of data ascertainment depended on the positive cohort member's living status, categorised as living, deceased or living-status-unknown. Sixty-one untraceable systemic sclerosis patients were assigned to the living-status-unknown category. Data collection for these and deceased systemic sclerosis patients were from patients' medical records.

Instruments

Living cohort-positive patients either participated (n=340), were unable to participate (due to senility, n=2) or refused to participate (n=19, including one terminally ill patient). Numerator and denominator data from interviewed positive and negative cohorts were obtained via telephone

TABLE 1
Questions used to Ascertain the Frequency of Familial Systemic Sclerosis Among a Systemic Sclerosis Cohort

1. 'How many . . . have you ever had?' (appropriating 'sisters and brothers', 'sons and daughters', 'grandchildren' and 'nieces and nephews' in turn)
2. 'How many uncles and aunts have you had?' (please don't include those who are related only by marriage)
3. 'Have (the relatives) had any illnesses? If so, what?'
4. 'Has anyone in the family had scleroderma? If yes, who?'

interviews using questions from a prepiloted questionnaire (Table 1).

As the systemic sclerosis cohort was more likely to overreport familial systemic sclerosis than were the negative cohort (reporting bias), the self-reported numerator data were subsequently validated either by clinical examination (HJE, NM, RW) or by review of the deceased relatives' medical records.

Data collection relating to subjective data were completed for the purposes of the doctoral analysis in March 1993, although data validation has continued until recently.

Statistics

The proportion with familial systemic sclerosis was expressed using the number of families at risk as the denominator.

Although both the number of second degree relatives and their frequency of systemic sclerosis were obtained, a decision was made to deal solely with first degree relatives' data, because these were felt to have greater validity. Of the negative cohorts' relatives, only one – an aunt – had systemic sclerosis. As a second degree relative she was therefore excluded from the relative risk analysis of familial disease among first degree relatives.

Chi-squared estimates were obtained for comparison of qualitative data in 2-by-x tables. The risk of systemic sclerosis in a subsequent first degree family member was compared to the risk of developing the disease in an initial first degree family member. This was expressed in terms of relative risk and the 95% confidence intervals were the Taylor Series 95% confidence limits.

Ethical Considerations

Study approval was granted from all the ethics committees of all the public hospitals and large private hospitals in Sydney, the Royal Australian College of General Practitioners, and the Royal Australasian Colleges of Physicians, and Surgeons.

TABLE 2
The Number of First Degree Relatives of Interviewed Positive and Negative Cohort Groups

	Positive cohort	Negative cohort
	n=340*	n=371
Fathers*	338	371
Mothers*	338	371
Brothers	560	549
Sisters	564	516
Sons	358	406
Daughters	328	412

*Two pairs of cohort-positive siblings account for the discrepancy between the total number of cohort-positive patients, and the total number of parents.

RESULTS

The distribution of first degree relatives among interviewed positive and negative cohort groups is listed in Table 2. It demonstrates a greater number of siblings and a lower number of offspring in the interviewed positive cohort than in the interviewed negative cohort. The gender distribution among the interviewed positive and negative cohorts' first degree relatives was comparable (p=0.99). As both cohorts were age-matched in the study design, the age distribution of their relatives was also assumed to be comparable.

Familial systemic sclerosis was ascertained and validated in four deceased patients from three families (Families one to three). It was also subjectively reported in 12 interviewed patients from ten families, and validated in nine from seven families (Families four to ten). Familial systemic sclerosis was overreported in three families including a cohort-positive female whose sister had Raynaud's but no skin involvement, a cohort-positive female whose mother died in her fifth decade of a poorly defined disease, possibly systemic sclerosis, and a cohort-positive female whose mother had Crohn's disease but no systemic sclerosis.

A summary of the ten cohort-positive families, their living status, gender, relationship, number of unaffected siblings, tissue typing results and disease subtype are displayed in Table 3. Included among these are three families (Families eight to ten) who were identified after March 1993, the completion time of subjective data collection. These were identified because a second family member developed and was diagnosed with the disease after this time. Further instances of familial disease may have also subsequently developed, of which the authors are unaware. Four instances of familial systemic sclerosis and

TABLE 3
Cases with Familial Disease – Data Relating to Living Status, Gender, Family Relationship and Disease Subtype

Family	Living status	Gender	Family member	Disease subtype	Unaffected siblings	Tissue typing
1	D	M	F	Ltd	?Si+?Br	
	D	M	So	Df	1Si+0Br	
2	D	F	M	Ltd	?Si+1Br	
	L	F	Da	Ltd	0Si+1Br	A3, 11 B14, 44 Dw4, 6 DR4, w6 DRw52, 53 DQw5, w32
3	D	F	M	Ltd	0Si+1Br	A3, 3 B7, 44 DR1, 15 DRw?,-DQ5, 6.1
	L	F	Da	Ltd	1Si+1Br	A3, 31 B7, 13 DR4, 15 DRw53,-DQ6.1.7
4	L(*D)	F	Si	Ltd	2Si+4Br	A2, 31 B13, 44 DR4,-DRw53,-DQA3,-
	L	F	Si	Ltd	2Si+4Br	A2, 31 B13, 44 DR4,-DRw53, DQA3,-
5	L	F	Si	Df	2Si+1Br	A24, 28 B18, 51 DR11, 13 DRw52,-DQ3,-
	L	F	Si	Df	2Si+1Br	A3, 24 B18, 51 DR11, 15 DRw52,-DQ5,7
6	L	F	Si	Ltd	1Si+2Br	A1, 28 B44, 57 DR1, 9 DRw53,-DQB3.5
	L (*D)	F	Si	Ltd	1Si+2Br	A1, 28 B44, 57 DR1, 9 DRw53,-DQB3.5
7	L	M	Br	Df	1Si+1Br	A11, 23 B44, 57 DR3, 13 DRw52,-DQ2, 6
	L	M	Br	Ltd	1Si+1Br	A3, 11 B35, 57 DR3, w13 DRw52,-DQ2, 6
8	D	F	M	Ltd	1Si+1Br	
	L	F	Da	Ltd	1Si+2Br	
9	D	F	M	Ltd	5Si+2Br	
	L	M	So	Ltd	0Si+3Br	
10	L	F	Si	Ltd	1Si+1Br	
	L (*D)	F	Si	Ltd	1Si+1Br	

L=living; D=deceased; L (*D)=living but subsequently died; M=male; F=female; F=father; M=mother; Br=brother, Si=sister, So=son; Da=daughter; Ltd=limited; Df=diffuse; ?Si=number of sisters not stated; ?Br=number of brothers not stated.
Families 3-6 and 15 have been previously reported as Families 4, 1, 2, 5 and 3 respectively.[26] The size of unaffected family members for Families 3 and 6 are as reported above, not as previously reported. Details from Family 7 have also recently been reported.[26]

three of localised disease in more distant relatives were also noted (Table 4). There were no reports of systemic sclerosis in the 371 negative cohorts' first degree relatives and only the one unvalidated report of systemic sclerosis in more distant relatives, a cohort-negative patient's maternal aunt.

Limited disease occurred in eight of the ten families. Observed disease subtype concordance was 80% (95% CI 44-97%) while expected concordance was 68%, well within the exact 95% confidence limits of the observed rate. The latter calculations were based on the observations that limited disease accounted for 80% of cases in the Sydney population.[27] Familial disease exhibited vertical transmission in five families, including three mother-daughter, one mother-son and one father-son combinations. Horizontal transmission occurred in five families, including four sister-sister, and one brother-brother combination. Females comprised 75% of involved cases.

Using the number of systemic sclerosis families as the denominator, the prevalence of familial systemic sclerosis among the systemic sclerosis cohort was 1.4% (95% CI: 0.8-2.2). This was in excess of the point prevalence of systemic sclerosis in the Sydney population, approximating 0.009% (0.008-0.010%)[27] and the prevalence of familial systemic sclerosis in the Sydney population approximating 1.4/million.

The relative risk of systemic sclerosis occurrence in a first degree family member could not be calculated, because a component of the relative risk denominator, the number of negative cohorts' first degree relatives with systemic sclerosis, was zero. Two estimates were made, however, in an effort to quantitate the relative risk. Addition of 0.033 (0.030, 0.037) to each cell (obtained by imposing the Sydney systemic sclerosis 1988 prevalence estimate on the 371 cohort-negative families) resulted in a relative risk estimate of 158 (zero to 644). (Relative risk estimates for the addition of 0.030 and 0.037 to each cell were 175 [56-543] and 142 [103-196] respectively.) Addition of 0.5 to each cell, a frequently used epidemiological tool, yielded a second relative risk estimate of 11.0 (2.7-19.3). This second estimate, however, assumed a systemic sclerosis prevalence in the cohort-negative families of 0.5/371.5, which published study estimates would consider unreasonably high.[28-31] In all probability, the first relative risk estimate, vastly higher in magnitude than the second, more closely approximates the truth. Although the relative risk was greatly increased, the absolute risk of systemic sclerosis among first degree family members remained small – 1.4% – as previously calculated.

Tissue typing results on a number of affected family members are listed in Table 3. The Class 2 antigen, DRw52, genetically linked to systemic

TABLE 4
Familial Disease in Other Family Members

Family	Gender	Relationship	Disease subtype	Comments
Cohort-positive				
11	F		Ltd	
	F	Niece*	Df	Validated
12	F		Df	
	F	2nd cousin	Df	Unvalidated
13	F		Ltd	
	?	1st cousin	?	Unvalidated
14	F		Ltd	
	F	Niece	?	Unvalidated
15[26]	F			
	F	Sister	Localised (morphea)	Validated
16	F		Ltd	
	F	Daughter	Localised	
17	F		Ltd	
	F	Mat aunt	Localised	
Cohort-negative				
1	F		NI	
	F	Aunt	?	Unvalidated

*Maternal half-sister's daughter.
F=female; Ltd=limited; Df=diffuse; ? Unknown; validated=disease objectively confirmed by clinical examination; unvalidated=disease diagnosis remains subjective, ie not objectively assessed to confirm diagnosis.

sclerosis, occurred in two of the six tissue typed families.

DISCUSSION

In 1958 Orabona and Albano published the first report of limited systemic sclerosis in two sisters.[3] Since then another 20 published cases unassociated with this study's cohort, have been reported,[4-25] including two from each of France and Japan,[21-24] and one from Russia.[19] These include 14 horizontal transmissions comprising eight sister-sister, three brother-brother, one sister-sister-sister, one brother-brother-sister, and one brother-sister-sister combinations. There are also seven reports of vertical transmission including five mother-daughter, one mother-son, one father-son combinations and no father-daughter combinations.

To the 21 reported cases of familial systemic sclerosis are added ten from the current study. These include five with horizontal transmission including four sister-sister and one brother-brother combinations, and five with vertical transmission, including three mother-daughter, one mother-son, one father-son and, again, no father-daughter combinations.

The gender ratio of affected members in familial disease was restricted to the current study because family structure was often not detailed in previous publications of familial disease.[3-5,7,11,12,14,17,19] Females accounted for 75% of familial disease, an occurrence in keeping with that found in the sporadic disease form.[32]

Limited disease occurred in eight of the ten families, again in keeping with the occurrence of limited disease in 80% of cases within Sydney.[27]

Observed and expected disease subtype concordance estimates were similar. Given the wide confidence intervals of the observed rates, interpretation of these findings must be viewed with caution.

Familial disease was observed less frequently in the medical records of deceased/living-status-unknown cases. The methodology differed by which data on family history of systemic sclerosis were collected, being routinely asked of all interviewed cases, but less routinely asked of non-interviewed cases. This difference in methodology may be sufficient to explain the apparent discrepancy in the prevalence of familial disease and, if true, may also explain the infrequency with which familial disease has been reported elsewhere.

Subjective reporting of familial systemic sclerosis was unable to be validated in three instances. Thus objective validation in family members, though time-consuming, was worthwhile. This study's most significant finding was the previously unquantitated relative risk in systemic sclerosis patients' first degree relatives. The estimated magnitude, an 11-158fold, increased risk, probably more truly approaches the upper than the lower figure, for reasons previously outlined. These findings are applicable to families of all systemic sclerosis patients, independent of gender, age or other disease determinants. Other disease determinants in which disease risk has been quantified include female gender, and silica exposure in males,[33-38] which approximate threefold and 25fold[38] increased risks. Like familial risk, the role of gender as a disease determinant is applicable to all systemic sclerosis patients. Silica exposure has thus far been causally associated only with systemic sclerosis in males, although this causal association has not been universally accepted. Many studies support the association while a well-designed comparative study from England refuted it.[39] Thus 75% of the total disease burden, that in females, remains largely unexplained.

The relative risk, as estimated from this study, does not necessarily imply a genetic role in the disease's aetiopathogenesis, because family members share not only common genetic material, but also common environmental exposures. This issue is currently being addressed in another study.

This study complements the literature in two respects. First, it adds substantially to the otherwise small list of documented cases. Second, it quantifies the risk of familial disease for the first time, supporting the claim that familial occurrence of systemic sclerosis is a disease determinant of considerable magnitude. ■

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